

Table X. Basis for allergen extract dosing recommendations

<p><b>Major allergen content:</b> Multiple studies demonstrate that the efficacious dose for allergen immunotherapy is between 5 and 20 µg of the major allergen per injection. Two extracts licensed in the United States are standardized based on major allergen content (measured by means of radial immunodiffusion): short ragweed (Amb a 1) and cat (Fel d 1). Patients might also have IgE sensitivity to multiple allergens in the extracts.</p>
<p>Currently, only the Amb a 1 and Fel d 1 FDA-issued radial immunodiffusion test reagents are standardized and used by all US manufacturers for short ragweed and cat hair and pelt extracts. The house dust mite, grass pollen, and dog hair major allergen assays are not standardized by the FDA and are either purchased or used internally by individual manufacturers.</p>
<p><b>Nonstandardized extracts:</b> The labeled concentrations for the nonstandardized extracts have no established standards for biologic potency. Nonstandardized extracts are labeled on the basis of PNU values or the weight of the source material extracted with a given volume of extracting fluid (wt/vol). There are no dose-response studies with nonstandardized extracts. When analyzed, the nonstandardized pollen extracts demonstrate potency that is similar to that of grass and ragweed, although with a wider range. A target dose of 0.5 mL of a 1:100 or 1:200 wt/vol of nonstandardized extract is reasonable.</p>
<p>Cockroach and mold/fungi extracts are generally of low potency and vary considerably in composition. Only glycerinated cockroach or mold/fungi extracts should be used, and they should be used at higher doses than the nonstandardized pollens.</p>
<p><b>Dust mites:</b> There are no dose-response studies with US-licensed dust mite extracts, and dosing recommendations in AUs are extrapolated from published European studies that use aqueous<sup>475</sup> and alum-precipitated extracts.<sup>[171] and [118]</sup> One study, designed to investigate the effect of 3 doses of an alum-precipitated <i>D pteronyssinus</i> extract (0.7, 7, and 21 µg of Der p 1), found a dose-response effect on efficacy and side effects.<sup>17</sup> The authors suggested that the optimal maintenance dose is 7 µg of Der p 1. Corresponding doses are based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as <i>D pteronyssinus</i> and <i>D farinae</i>.</p>
<p><b>Cat hair and pelt:</b> The major cat allergen Fel d 1 is reported in FDA units (Fel d 1 U) with 1 Fel d 1 U equal to approximately 2 to 4 µg of Fel d 1.<sup>[370], [374] and [476]</sup> The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 U to 19.9 U/mL. One study demonstrates clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 (or highest tolerated) dose in terms of decreased cat extract PD<sub>20</sub>, titrated skin test results, and allergen-specific IgE and IgG.<sup>[332] and [333]</sup> In a study that investigated the efficacy in terms of immunologic changes of 3 doses of a US-licensed cat extract (0.6, 3, and 15 µg of Fel d 1 from ALK-Abelló, Round Rock, Tex) there was significant effect on titrated skin prick tests, allergen-specific IgG4 levels, and CD4<sup>+</sup>/IL-4 only in the group treated with 15 µg of Fel d 1, although the 3-µg dose group did demonstrate a significant change in titrated skin test response and an increase in cat-specific IgG4 levels.<sup>18</sup></p>
<p><b>Grass:</b> There have been no dose-response studies with US-licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,<sup>99</sup> alum-precipitated,<sup>[20] and [128]</sup> and calcium phosphate-precipitated grass pollen extracts.<sup>477</sup> One of these studies compared a dose of 2 µg with 20 µg of major timothy grass allergen (Phl p 5) and found clinical efficacy at both doses.<sup>20</sup> The efficacy was greater in the dose of 20 µg of Phl p 5, but the systemic reaction rate was also higher in the high-dose group. The package inserts for US-licensed grass pollen extracts contain a table to convert the nonstandardized units (wt/vol and PNU) for which there have been studies that have demonstrated efficacy into BAUs. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as the Northern pasture grasses (subfamily Pooideae; eg, perennial rye, meadow fescue, or timothy).</p>
<p><b>Bermuda grass:</b> Bermuda grass has an assigned potency of 10,000 BAU, which is 10-fold less than the other standardized grasses. However, the major allergen content of Bermuda grass according to one extract manufacturer (ALK-Abelló) was 348 µg/mL of Cyn d 1 with a range of 141 to 422 µg/mL, and this is similar to the major allergen content of the other standardized grasses.<sup>478</sup> It has been speculated that the apparent discrepancy in assigned potency to Bermuda grass extract was the result of standardization (ID<sub>50</sub>EAL testing)</p>

undertaken in a nonendemic area for Bermuda grass.

**Short ragweed:** Short ragweed is reported in FDA units, with 1 U of Amb a 1 equaling 1 µg of Amb a 1. The potency units for short ragweed extracts were originally assigned based on their Amb a 1 content. Subsequent data suggest that 1 U of Amb a 1 is equivalent to 1 µg of Amb a 1, and 350 Amb a 1 U/mL is approximately equivalent to 100,000 AU/mL.<sup>376</sup> The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2,000 AU, with a range of 1,000 to 4,000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrates a significant improvement in ragweed nasal challenge in patients treated with a mean dose of 6 µg of Amb a 1 for 3 to 5 years compared with an untreated matched control group.<sup>479</sup> A ragweed dose-response study (0.6, 12.4, and 24.8 µg Amb a 1) demonstrates efficacy as measured by nasal challenge at 12 and 24 µg Amb a 1.<sup>97</sup> The efficacy of the 24-µg dose was not significantly better than that of the 12-µg dose, and the authors concluded that the optimal dose for ragweed extract is greater than 0.6 µg but not more than 12.4 µg of Amb a 1.

**Dog hair or pelt extracts:** Dog hair or pelt extracts are not standardized, and potency is reported as wt/vol or PNU per milliliter. One dose-response study with a US-licensed dog hair extract investigated the efficacy of 3 doses (AP dog hair; Hollister-Stier; 0.6, 3, and 15 µg of Can f 1) in terms of immunologic changes and found the dose of 15 µg of Can f 1 to be most efficacious.<sup>21</sup> The 3-µg dose also demonstrated significant efficacy, although not as great as the 15-µg dose. The extract used in the dosing study was assayed at 160 µg/mL. Subsequent lots assayed ranged between 80.4 and 396.3 µg/mL Can f 1 (110 lots; mean of 170.8 µg/mL Can f 1 [SD, 52.3 µg/mL]); information provided by the extract manufacturer, Hollister-Stier, by using references calibrated back to Indoor Biotechnologies ST-CF1 standard to maintain consistency with original clinical trial recommendations.

**Hymenoptera venom:** The recommended maintenance dose for stinging Hymenoptera venom immunotherapy is 100 µg of each insect venom.<sup>158</sup> However, there is some controversy about the optimum maintenance dose. Initial studies used 100 µg as the maintenance dose. One investigator has used the 50-µg maintenance dose in patients with yellow jacket allergy successfully,<sup>147</sup> although some believe that this dose offers a lesser degree of protection. Increasing the maintenance dose up to 200 µg per dose has been effective in achieving protection in some patients who have experienced sting reactions while receiving a 100-µg maintenance dose of VIT.<sup>421</sup> (see “Stinging insect hypersensitivity: a practice parameter update II” for a more detailed discussion of venom and imported fire ant immunotherapy dosing).

**Imported fire ant:** The optimal dose for fire ant whole-body extract immunotherapy is less well defined. Most reports have recommended 0.5 mL of a 1:100 wt/vol extract with either *Solenopsis invicta* or a mixture of *Solenopsis invicta* and *Solenopsis richteri* extract, although there are some recommendations for a dose as high as 0.5 mL of a 1:10 wt/vol extract.<sup>[122], [123], [152] and [298]</sup>